IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**U.S. Patent No. Re38,115 (a reissue of U.S. Patent No. 5,863,927)**
Inventors:	SMITH, Richard Alan, et al.
Original Issue Date:	January 26, 1999
Reissue Issue Date:	May 6, 2003
For:	DEXTROMETHORPHAN AND AN OXIDASE INHIBITOR FOR TREATING INTRACTABLE CONDITIONS
Assignee:	Center for Neurologic Study
Date:	December 17, 2010
Attorney Docket:	36967-0001-1
NDA:	**NDA 21-879 (NUEDEXTA™ capsule)**

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL FOR APPLICATION FOR EXTENSION OF PATENT

Sir:

Transmitted herewith for filing is an Application For Extension of Patent Term Under 35 U.S.C. §156 with respect to the above-identified patent.

Applicant, the assignee of the above-referenced patent, on this day has filed simultaneously two related applications for extension of patent term under 35 U.S.C. §156, including the present application referenced in the header above. These two patent term extension applications relate to U.S. Patent nos. Re38,551 and 5,206,248, both for the regulatory review period ending with the FDA approval for New Drug Application no. NDA 21-879.

Applicant respectfully requests that if the Commissioner determines that both of U.S. Patent nos. Re38,115 and 5,206,248 are entitled to a patent term extension under the same regulatory review period, that the Commissioner establish a time period in accord with the policies set forth in MPEP § 2761 within which the Applicant will be permitted to elect the patent for which extension is desired and/or to voluntarily withdraw an application. At that time, Applicant will elect and/or withdraw any applications for patent term extension, as appropriate, to ensure that only one patent is extended for the subject regulatory review period in accord with 35 U.S.C. § 156.

Applicant respectfully requests that if the Commissioner does not share Applicant's view that it is entitled under 35 U.S.C. § 156 to extend the subject patent, that the Commissioner direct the Office to contact the undersigned attorney.

In light of the above, and in accordance with the requirements of 35 U.S.C. § 156, attached for the patent and NDA approval identified in the above header are the following:

1) Application For Extension of Patent Term (including Exhibits A-F) – application 14 pages and Exhibits 34 pages for 48 pages total;

2) Extra copy 1 of Application for Extension of Patent Term (including Exhibits A-F) – application 14 pages and Exhibits 34 pages for 48 pages total; and

3) Extra copy 2 of Application for Extension of Patent Term (including Exhibits A-F) – application 14 pages and Exhibits 34 pages for 48 pages total.

☒ Please charge my Deposit Account No. 50-1349 the amount of $1,120.00, which is believed to be the appropriate fee for a patent term extension as established by 37 C.F.R. § 1.20(j),.

☒ The Commissioner is hereby authorized to charge payment of any fees associated with or necessary for the prosecution of this patent term extension application, including debiting any deficit or crediting any overpayment relating to the fee identified above, to Deposit Account No. 50-1349.

Respectfully submitted,
Hogan Lovells US LLP

Dated: December 17, 2010

By: _____
Kevin G. Shaw
Registration No. 43,110

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**U.S. Patent No. Re38,115 (a reissue of U.S. Patent No. 5,863,927)**
Inventors:	SMITH, Richard Alan, et al.
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APPLICATION FOR EXTENSION OF PATENT

TERM UNDER 35 U.S.C. §156

Commissioner for Patents:

Center of Neurologic Study ("Center"), a non-profit organized and existing under the laws of the state of California, and having a principal place of business at 9850 Genesee Ave, Suite 320, La Jolla, CA, 92037, is the owner of the entire interest in and to U.S. Patent No. Re38,115, granted to Richard Alan Smith and Jonathan M. Licht for "Dextromethorphan and an Oxidase Inhibitor for Treating Intractable Conditions," as reflected in the assignment document recorded by the U.S. Patent and Trademark Office on March 23, 1998 at Reel 009068, Frame 0121, against U.S. Patent No. 5,863,927 (of which U.S. Patent No. Re38,115 is a reissue patent). Attached at **Exhibit A** is an Appointment of Agent document reflecting that Applicant, AVANIR Pharmaceuticals, Inc. ("AVANIR"), has been appointed by Center as its fully qualified agent to

prosecute any and all patent term extension applications regarding U.S. Patent No. Re38,115 and to transact all business in the Patent and Trademark Office connected therewith.

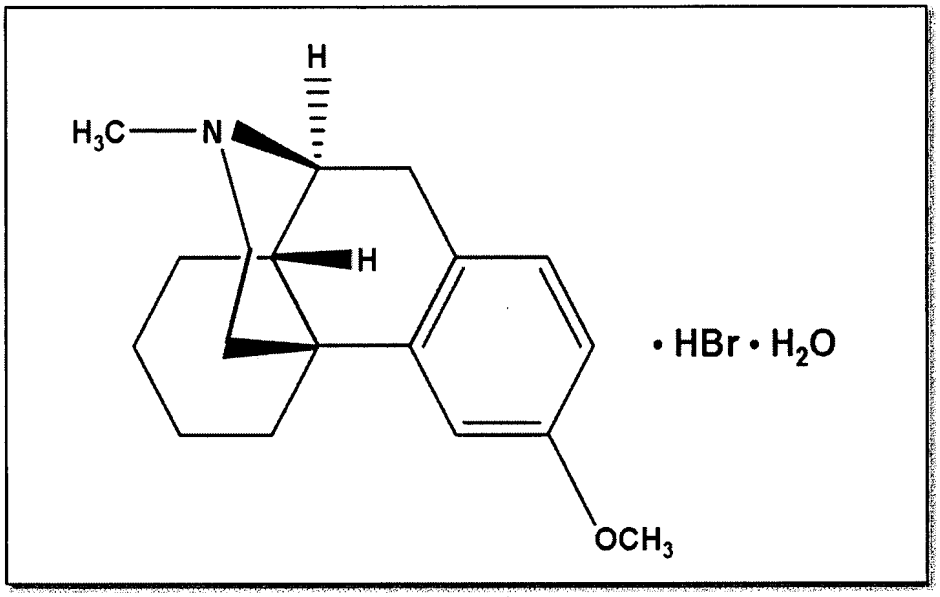
AVANIR, a corporation of the state of California and having a place of business at 101 Enterprise, Suite 300, Aliso Viejo, CA 92656, is the owner of a New Drug Application ("NDA") for NUEDEXTA™ capsule, NDA number NDA 21-879. Applicant AVANIR also exclusively licenses rights under U.S. Patent No. Re38,115. Thus, AVANIR has the right to rely upon NDA 21-879 supporting FDA approval of NUEDEXTA™ capsule and the right to file applications with the United States Patent and Trademark Office for purposes of obtaining any and all patent term extensions available for U.S. Patent No. Re38,115 in conjunction with the approval of NUEDEXTA™ capsule. Attached at **Exhibit B** is a Power of Attorney document from AVANIR to the undersigned attorney.

Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156, based upon the approval by the Food and Drug Administration for commercial marketing or use of NUEDEXTA™ capsule, since the active ingredients of NUEDEXTA™ capsule are dextromethorphan hydrobromide and quinidine sulfate, and those active ingredients fall within the ambit of various claims of U.S. Patent No. Re38,115. The information contained in this Application and its Exhibits is provided in accordance with the rules promulgated by the U.S. Patent and Trademark Office at 37 CFR §§1.710-1.785 and presented in the manner set forth at 37 CFR §1.740.

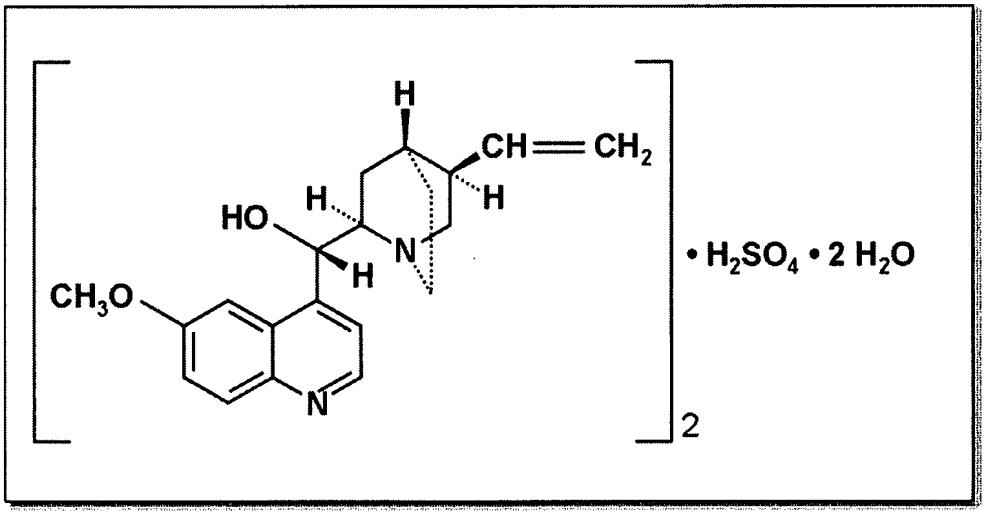
1. A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product, NUEDEXTA™ capsule, is an oral formulation that contains dextromethorphan hydrobromide and quinidine sulfate in a fixed dose composition and is indicated for the treatment of pseudobulbar affect ("PBA"). Dextromethorphan hydrobromide is the pharmacologically active ingredient that acts on the central nervous system, while quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism that increases the systemic bioavailability of dextromethorphan. The IUPAC chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-,(9α, 13α, 14α), hydrobromide, or, alternatively, (+) -3-methoxy-N-mehtylmorphinan hydrobromide. The

dextromethorphan hydrobromide is present in the form of a monohydrate, which monohydrate has the empirical formula $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and has a molecular weight of 370.33. Dextromethorphan hydrobromide monohydrate has the structural formula:



Quinidine sulfate has the IUPAC chemical of cinchonan-9-01, 6'-methoxy-, (9S) sulfate (2:1), (salt). The quinidine sulfate is present in the form of a dihydrate, which dihydrate has the empirical formula $2C_{20}H_{24}N_2O_2 \cdot H_2SO_4 \cdot 2H_2O$ and has a molecular weight of 782.96. The structural formula of quinidine sulfate dihydrate is:



The combination product of dextromethorphan hydrobromide hydrate and quinidine sulfate dihydrate is prepared as a white to off-white powder that is sparingly soluble in acetonitrile and ethanol. The approved product is formulated as capsules for oral administration that each provide a fixed dosage of 20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate. NUEDEXTA™ capsules contain the following inactive ingredients: croscarmellose sodium NF, microcrystalline cellulose NF, colloidal silicon dioxide NF, lactose monohydrate NF, and magnesium stearate NF.

2. A Complete Identification Of The Federal Statute Including The Applicable Provisions Of Law Under Which The Regulatory Review Occurred

The approved product, NUEDEXTA™ capsule, was subject to regulatory review under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355).

3. An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

The approved product, NUEDEXTA™ capsule, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355) on October 29, 2010. A copy of a letter from the Food and Drug Administration ("FDA") indicating the date of approval is attached hereto at **Exhibit C**.

4. In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, and Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The active ingredients in NUEDEXTA™ capsule are dextromethorphan hydrobromide and quinidine sulfate. The commercial marketing or use of the product NUEDEXTA™ (dextromethorphan hydrobromide and quinidine sulfate) capsules after the regulatory review period is the first permitted commercial marketing or use of dextromethorphan hydrobromide under the provision of the Federal Food, Drug, and Cosmetic Act, the Public

Health Service Act, or the Virus-Serum-Toxin Act, under which such regulatory review period occurred.

5. A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to 37 CFR §1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is December 28, 2010.

6. A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of The Inventor, The Patent Number, The Date Of Issue, And The Date Of Expiration

The complete identification of the patent for which extension is sought is:

Inventors:	Richard Alan Smith, and Jonathan M. Licht
Patent Number:	Re38,115 (a reissue of 5,863,927)
Issue Date of 5,863,927:	January 26, 1999
Issue Date of Re38,115:	May 6, 2003
Expiration Date:	January 26, 2016 (without extension under 35 U.S.C. §156)

7. A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A complete copy of U.S. Patent No. Re38,115 is annexed as **Exhibit D**.

8. A Copy Of Any Disclaimer, Certificate of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In The Patent

The patent for which extension is being sought has not been the subject of any disclaimer, reexamination certificate, or certificate of correction. The scheduled maintenance fees for U.S. Patent Re38,115 were duly paid. The first maintenance fee was duly paid on February 11, 2002 by Applicant (for U.S. Patent 5,863,927), the second maintenance fee was duly paid on April 6, 2006 by Applicant, and the third and final maintenance fee was duly paid on July 27, 2010 by Applicant. No further maintenance fees are due. Copies of the maintenance fee statements evidencing past payments are annexed as **Exhibit E**.

9. A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which At Least One Such Patent Claim Reads On The Approved Product Or Method Of Using Or Manufacturing The Approved Product

U.S. Patent No. Re38,115 claims the approved product, NUEDEXTA™ capsule. More specifically, claims 18-21 cover unit dosage formulations. A representative claim is compared to the approved product in the table below.

Patent Claim	Approved Product
18. A unit dosage formulation for treatment of chronic or intractable pain, comprising: (a) dextromethorphan or a pharmaceutically acceptable salt thereof, and, (b) a debrisoquin hydroxylase inhibitor, in a combined form that is designed for oral ingestion by humans, wherein the dextromethorphan or salt thereof and the debrisoquin hydroxylase inhibitor are present at a combined dosage which renders the dextromethorphan therapeutically effective in substantially reducing chronic or intractable pain, without causing unacceptable side effects.	The approved product is an oral capsule that includes a therapeutically effective quantity of dextromethorphan hydrobromide, which is a pharmaceutically acceptable salt of dextromethorphan. The approved product also includes a therapeutically effective quantity of quinidine sulfate, which is a debrisoquin hydroxylase inhibitor (see dependent claim 20). The approved product is a capsule formulation containing a unit dosage comprising 20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate. This combined dosage has been reported to reduce bodily pain in patients receiving the dosage to treat pseudobulbar affect.

10. A Statement, Beginning On A New Page, Of The Relevant Dates And Information Pursuant To 35 U.S.C. § 156(g) In Order To Enable The Secretary Of Agriculture, As Appropriate, To Determine The Applicable Regulatory Review Period As Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, Or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) Or A Product License Application (PLA) Was Initially Submitted And The NDA Or PLA Number And The Date On Which The NDA Was Approved Or The Product License Issued

The IND for NUEDEXTA™ capsule (IND 56,954) was submitted on September 21, 1998, and by rule became effective 30 days later on October 21, 1998. For purposes of this application for patent term extension, the Applicant believes it is entitled to an IND date of at least as early as October 21, 1998. The NDA (NDA 21-879) for NUEDEXTA™ capsule was initially submitted to the Food and Drug Administration on January 27, 2006 and was approved on October 29, 2010.

11. A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A brief description of significant activities undertaken by the marketing applicant during the regulatory review period with respect to the approved product is provided below. Also, a description of various clinical trials conducted by Applicant is annexed as **Exhibit F**.

The list below in conjunction with **Exhibit F** provides a chronology of the major communications between the marketing applicant and the Food and Drug Administration, including a brief summary of the subject matter and date of these communications.

Applicant reserves the right to supplement the chronology with materials from which it was derived or other evidence related to Applicant's conduct in obtaining the approval of NUEDEXTA™ capsule. *See, e.g.*, 21 CFR § 60.32.

· IND 56,954 Submitted	Sept. 21, 1998
· IND 56,954 Effective	Oct. 21, 1998
· Enrollment of first phase 3 study complete*	June 2002
· End of Phase 2 Meeting	Aug. 15, 2002
· Enrollment of second phase 3 study complete*	March 2004
· Pre-NDA Meeting	May 17, 2004
· NDA 21,879 Submitted	Jan. 27, 2006
· Received approvable letter	Oct. 30, 2006
· Post-action Meeting	Feb. 26, 2007
· Special Protocol Assessment Meeting	Jul. 16, 2007
· Enrollment of third phase 3 study complete*	March 2004
· NDA 21,879 Re-Submitted (complete response filed)	Apr. 30, 2010
· FDA approves NDA 21,879	Oct. 29, 2010

* See **Exhibit G** for more information concerning clinical trials

12. A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Applicant is of the opinion that U.S. Patent No. Re38,115 is eligible for extension under 35 U.S.C. § 156, because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. §156(a); 37 CFR §1.720(a)

U.S. Patent No. Re38,115 claims methods of using the approved product.

b. 35 U.S.C. §156(a)(1); 37 CFR §1.720(g)

The term of U.S. Patent No. Re38,115 has not expired before submission of this application.

c. 35 U.S.C. §156(a)(2); 37 CFR §1.720(b)

The term of U.S. Patent No. Re38,115 has never previously been extended under 35 U.S.C. §156.

d. 35 U.S.C. §156(a)(3); 37 CFR §1.730

This application for extension is submitted by the authorized agent or the owner of record in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office.

e. 35 U.S.C. §156(a)(4); 37 CFR §1.720(d)

The product NUEDEXTA™ capsule has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use.

f. 35 U.S.C. §156(a)(5)(A); 37 CFR §1.720(e)(i)

The commercial marketing or use of the product NUEDEXTA™ (dextromethorphan hydrobromide and quinidine sulfate) capsules after the regulatory review period is the first permitted commercial marketing or use of dextromethorphan hydrobromide under the provision of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. §355) under which such regulatory review period occurred. Applicant acknowledges that dextromethorphan-containing products have previously been sold in the United States. However, the approval of dextromethorphan hydrobromide in NUEDEXTA™ constitutes the "first permitted commercial marketing or use of the product under the provision of law under which said regulatory review period occurred" (35 U.S.C. § 156(a)(5)(A)).

The provision of law under which the dextromethorphan hydrobromide active ingredient in NUEDEXTA™ was subject to a regulatory review period is section 505 of the FFDCA as amended by the Drug Price Competition and Patent Term Restoration Act of 1984. To the best of Applicant's knowledge, dextromethorphan-containing products sold prior to 1962 were not subject to a "regulatory review period" as defined under section 156(g), and were permitted to be marketed under a provision of law different from the provision of law under which NUEDEXTA™ was studied, reviewed, and approved. To the best of Applicant's knowledge, dextromethorphan-containing products sold after 1962 have been marketed under the Food and Drug Administration's Over-the-Counter Drug Review, and not under the provision of law under which NUEDEXTA™ was studied, reviewed, and approved.

Applicant is aware of the decision in *Westwood v. Quigg*, 13 U.S.P.Q.2d 2067 (D.D.C. 1989), which affirmed a denial by the U.S. Patent and Trademark Office of a patent term extension application for a

drug that first came to market before 1962. However, Applicant maintains that *Westwood* was wrongly decided, is distinguishable, and would not withstand scrutiny today. Among other reasons, the court erred in failing to apply the FFDCA as it existed at the time it was amended by the Drug Price Competition and Patent Term Restoration Act of 1984.

g. 35 U.S.C. §156(c)(4); 37 CFR §1.720(h)

No other patent has been extended for the same regulatory review period for the product NUEDEXTA™ capsule.

h. 35 U.S.C. §156(d)(1); 37 CFR §1.720(f)

This application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use.

Applicant is of the opinion that U.S. Patent No. Re38,115 is eligible for extension under 35 U.S.C. § 156 for 5 years, or 1828 days, as determined pursuant to 37 CFR §1.775 as follows:

Patent Information:

Patent 5,863,927 Issue Date	January 26, 1999
PCT filing date	September 22, 1994
Term adjustment (days) granted under 35 U.S.C. 154(b)	0
Current Patent Expiration Date (17 year term)	January 26, 2016

FDA Information:

Date IND Becomes Effective	October 21, 1998
Date NDA Submitted to the FDA	January 27, 2006
Date NDA Approved by the FDA	October 29, 2010

Regulatory Review and IND Periods:

Start Date of Regulatory Review Period	October 21, 1998
End Date of Regulatory Review Period	October 29, 2010
Total Review Period (# days Oct. 21, 1998 to Oct. 29, 2010)	4392
IND Period (# days Oct. 21, 1998 to Jan. 30, 2006)	2659
½ IND Period (# days)	1330

Regulatory Review Period Allowed:

Total Regulatory Review Period (# days)	4392
less days before patent granted (# days)	- 98
less ½ IND period (# days)	- 1330
Total Days Allowed from Regulatory Review Period	**2964 days**
Date 2964 days from Current Patent Expiration Date ("Date 1")	March 8, 2024

Statutory Limitations:

5 year extension limitation ("Date 2")	January 26, 2021
14 years from NDA approval limitation ("Date 3")	October 30, 2024

Expiration Date (Earliest of Date 1, Date 2, or Date 3): January 26, 2021

Maximum Extension in Days: 1828

13. A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations of entitlement to the extension sought in the Application.

14. The Prescribed Fee For Receiving And Acting Upon The Application For Extension

The prescribed fee pursuant to 37 CFR §1.20(j) for receiving and acting upon this application is to be charged to the Deposit Account of Applicant's undersigned attorney as authorized in the attached letter.

15. The Name, Address, And Telephone Number Of The Person To Whom Inquiries And Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Please address all correspondence to:

Kevin G. Shaw
Hogan Lovells US, LLP
555 Thirteenth St., NW
Washington, DC 20004
(202) 637-6466

16. A Duplicate Of The Application Papers, Certified As Such

Applicant hereby certifies that this application for extension is being filed in triplicate.

17. An Oath Or Declaration

Applicant, through its undersigned patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the agent or owner to act on behalf of the agent or owner in patent matters, being duly warned that willful false statements are punishable by fine or imprisonment or both under section 1001 of Title 18, United States Code and that willful false statements and the like may jeopardize the validity of this application and the patent to which it relates, states and declares that the following statements made based on his own knowledge are true and that all statements made on information and belief are believed to be true:

(1) The undersigned is registered to practice before the Patent and Trademark Office and is making this declaration as a patent attorney who has general authority to act on behalf of the applicant in patent matters.

(2) The undersigned has reviewed and understands the contents of the application being submitted pursuant to this section;

(3) The undersigned believes the patent is subject to an extension pursuant to 37 C.F.R. § 1.710 in the event of NDA approval and, in the interim, is subject to an extension pursuant to 37 C.F.R. § 1.790;

(4) The undersigned believes an extension of the length claimed is justified under 35 U.S.C. 156 and the applicable regulations; and

(5) The undersigned believes the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720 in the event of NDA approval, and meets the requirements for an interim extension of a patent set forth in 37 C.F.R. § 1.790.

If this application for extension of patent term is held to be informal, applicant may seek to have that holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. §§ 1.181, 1.182 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Respectfully submitted,

Dated: December 17, 2010

By: _____
Kevin G. Shaw
Registration No. 43,110

HOGAN LOVELLS US LLP
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Facsimile: 202-637-5910
Email: kevin.shaw@hoganlovells.com
Customer No.: 24633

Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**U.S. Patent No. Re38,115 (a reissue of U.S. Patent No. 5,863,927)**
Inventors:	SMITH, Richard Alan, et al.
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Attorney Docket:	36967-0001-1
NDA:	**NDA 21-879 (NUEDEXTA™ capsule)**

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Commissioner for Patents
P.O. Box 1450
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APPOINTMENT OF AGENT FOR PATENT TERM EXTENSION APPLICATION

The Center for Neurologic Study ("CNS"), a non-profit organized and existing under the laws of California, and having a principal place of business at 9850 Genesee Ave., Suite 320, La Jolla, CA, 92037, is the sole owner of the entire interest in and to U.S. Patent No. Re38,115, granted to Richard Alan Smith and Jonathan M. Licht for "Dextromethorphan and an Oxidase Inhibitor for Treating Intractable Conditions," as reflected in the assignment document recorded by the U.S. Patent and Trademark Office on March 23, 1998 at Reel 009068, Frame 0121, against U.S. Patent No. 5,863,927 (of which U.S. Patent No. Re38,115 is a reissue patent). CNS has licensed U.S. Patent Re38,115 to AVANIR Pharmaceuticals, Inc. ("AVANIR"), a corporation of the state of California and having a place of business at 101 Enterprise, Suite 300, Aliso Viejo, CA 92656, as has appointed and does hereby appoint AVANIR as its fully qualified

agent to prosecute any and all patent term extension applications regarding U.S. Patent No. Re38,115 and to transact all business in the Patent and Trademark Office connected therewith.

The undersigned, acting in the official capacity stated below, has authority to and does hereby execute this document on behalf of CNS.

Richard Allan Smith 12/13/2010

Dr. Richard A. Smith
Director
Center For Neurologic Study
9850 Genesee Ave., Suite 320
La Jolla, CA 92037

Date

Exhibit B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**U.S. Patent No. Re38,115 (a reissue of U.S. Patent No. 5,863,927)**
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Assignee:	Center for Neurologic Study
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POWER OF ATTORNEY FOR PATENT TERM EXTENSION APPLICATION

The Center for Neurologic Study ("CNS"), a non-profit organized and existing under the laws of California, and having a principal place of business at 9850 Genesee Ave, Suite 320, La Jolla, CA, 92037, is the sole owner of the entire interest in and to U.S. Patent No. Re38,115, granted to Richard Alan Smith and Jonathan M. Licht for "Dextromethorphan and an Oxidase Inhibitor for Treating Intractable Conditions," as reflected in the assignment document recorded by the U.S. Patent and Trademark Office on March 23, 1998 at Reel 009068, Frame 0121, against U.S. Patent No. 5,863,927 (of which U.S. Patent No. Re38,115 is a reissue patent). Attached at Exhibit A of the attached Patent Term Extension Application submitted in the United States Patent and Trademark Office for the above-referenced patent and NDA is an Appointment of Agent document reflecting that AVANIR Pharmaceuticals, Inc. ("AVANIR"), a corporation

of the state of California and having a place of business at 101 Enterprise, Suite 300, Aliso Viejo, CA 92656, has been appointed by CNS as its fully qualified agent to prosecute any and all patent term extension applications regarding U.S. Patent No. Re38,115 and to transact all business in the Patent and Trademark Office connected therewith.

AVANIR, in this duly-authorized legal capacity, hereby appoints Kevin G. Shaw and the registered practitioners of Hogan Lovells US, LLP included in the Customer Number provided below to prosecute this patent term extension application and to transact all business in the Patent and Trademark Office connected therewith, and further directs that all correspondence regarding the extension application be addressed to Kevin G. Shaw at that Customer Number.

The undersigned, acting in the official capacity stated below, has authority to does hereby execute this document on behalf of AVANIR.

Customer Number: 24633

Please direct all inquiries to:

Kevin G. Shaw
Telephone: (202) 637-6466
Facsimile: (202) 637-5910

Gregory J. Flesher
Vice President, Business Development
AVANIR Pharmaceuticals, Inc.

12/16/10
Date

Exhibit C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021879

NDA APPROVAL

Avanir Pharmaceuticals
Attention: Randall Kaye, M.D.
Vice President, Clinical and Medical Affairs
101 Enterprise, Suite 300
Aliso Viejo, CA 92656

Dear Dr. Kaye:

Please refer to your New Drug Application (NDA) dated January 27, 2006, received January 30, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) Capsules.

We acknowledge receipt of your amendments dated April 30, May 5, June 29, July 16, 19, and 21, August 6 and 23, September 1, 16, and 21, and October 6, 27, and 28, 2010.

The April 30, 2010, submission constituted a complete response to our October 30, 2006, action letter.

This new drug application provides for the use of Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) Capsules for the treatment of pseudobulbar affect (PBA).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of

Labeling Technical Qs and As" at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels, dated October 27, 2010, revised as agreed upon in an October 28, 2010 electronic mail message from Art Rosenthal of Avanir, as soon as they are available, but no more than 30 days after they are printed. The revisions that were agreed upon include:

A. All Container Labels and Carton Labeling

1. As currently presented, the font type and weight used for the established name and dosage form make them appear less than ½ the size of the proprietary name. Ensure the established name is printed in letters that are at least ½ as large as the letters comprising the proprietary name. Additionally, the established name should have a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)]. Ensure the dosage form statement is the same size, type, font, etc. as the established name.

2. In the established name, the two active ingredients are separated by a forward slash (/). Replace the forward slash with the word "and" (i.e., dextromethorphan HBr and quinidine sulfate).

3. In the "Each capsule contains" statement, connect the two active ingredients with the word "and" (i.e., 20 mg of dextromethorphan hydrobromide and 10 mg of quinidine sulfate).

4. As currently presented, the bolded, green net quantity statement is as prominent as the proprietary name. Decrease the prominence of the net quantity statement by revising the color (e.g., white font) and debolding.

B. Container Label (Trade)

1. Relocate the strength to appear immediately below the proprietary and established names (as presented on the carton labeling). You may have to delete the blue/green graphic, which is as prominent as the strength, in order to accomplish this. The proprietary name, established name and strength should be the most prominent information on the principal display panel.

2. Relocate the 'Each capsule...' statement to the side panel, which is the usual customary location for this statement.

C. Container Label (Professional Sample)

Relocate the strength to appear immediately below the proprietary and established names (as presented on the carton labeling). You may have to delete the blue/green graphic, which is as prominent as the strength, in order to accomplish this. The proprietary name, established name and strength should be the most prominent information on the principal display panel.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021879**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRATION DATING

A 24 month expiration dating period is granted for Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) Capsules, dextromethorphan 20mg and quinidine 10 mg.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for birth to two years of age years because necessary studies are impossible or highly impracticable. This is because PBA involves exaggerated or contradictory episodes of laughing or crying given the patient's actual emotional state. In children age 2 and younger, verbal and non-verbal communication is not adequately developed to allow for accurate appraisal of the patient's actual emotional state, such that the condition cannot be diagnosed.

We are deferring submission of your pediatric studies for ages 2 to 16 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must

be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1702-1 Conduct a pharmacokinetic dose-ranging and safety study in patients 2 to 16 years of age with PBA.

Final Protocol Submission:	10/2011
Study/Trial Completion:	04/2013
Final Report Submission:	10/2013

1702-2 Conduct a Phase 3, 12-week, multiple center, double-blind, placebo-controlled efficacy and safety study in pediatric patients 2 to 16 years of age with PBA.

Final Protocol Submission:	10/2013
Study/Trial Completion:	04/2015
Final Report Submission:	10/2015

1702-3 Conduct a Phase 3 open-label extension safety study in pediatric patients 2 to 16 years of age with PBA.

Final Protocol Submission:	10/2013
Study/Trial Completion:	04/2015
Final Report Submission:	10/2015

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of neuronal degeneration, prenatal developmental, reproductive and neurobehavioral toxicity, and adverse effects of dextromethorphan/quinidine on postnatal growth and development. In addition, an analysis of spontaneous postmarketing adverse events will not be sufficient to identify unexpected serious risks related to the potential for quinidine to act at the $5HT_{2B}$ receptor that could result in the serious risk of cardiac valvulopathy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1702-4 - A juvenile neurotoxicity study in neonatal rats intended to assess the potential for Nuedexta to induce apoptotic neuronal degeneration in the human fetus. Dextromethorphan/quinidine should be administered during the postnatal period demonstrated to be the most vulnerable to this lesion.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2011
Study Completion:	06/2012
Final Report Submission:	09/2012

1702-5 - A pre- and post-natal development (including maternal function) study in rats, testing doses up to a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2011
Study Completion:	01/2012
Final Report Submission:	04/2012

1702-6 - An embryo-fetal development study in rabbits, testing doses up to a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2011
Study Completion:	07/2011
Final Report Submission:	10/2011

1702-7 - A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of dextromethorphan/quinidine on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of dextromethorphan/quinidine on growth, reproductive development, and neurological and neurobehavioral development.

The timetable you submitted on 10/25/2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2011
Study Completion:	07/2012
Final Report Submission:	12/2012

1702-8 - Studies to assess the *in vitro* binding affinity and functional activity of quinidine at the $5HT_{2B}$ receptor.

The timetable you submitted on 10/29/10 states that you will conduct these studies according to the following schedule:

Final Protocol Submission:	02/28/11
Study Completion:	08/31/11
Final Report Submission:	11/30/11

1702-9 - If quinidine is confirmed to be a $5HT_{2B}$ agonist, then an investigative study to assess the potential for quinidine to induce cardiac valvulopathy will be needed.

The timetable you submitted on 10/29/10 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/30/12
Study Completion:	03/30/13
Final Report Submission:	06/30/13

Submit all protocols to your IND 056954, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also

include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your voluntary submission dated April 30, 2010, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
10/29/2010

Exhibit D

US00RE38115E

(19) **United States**

(12) **Reissued Patent**

Smith et al.

(10) **Patent Number: US RE38,115 E**

(45) **Date of Reissued Patent: May 6, 2003**

(54) **DEXTROMETHORPHAN AND AN OXIDASE INHIBITOR FOR TREATING INTRACTABLE CONDITIONS**

(75) Inventors: **Richard Alan Smith**, La Jolla, CA (US); **Jonathan M. Licht**, San Diego, CA (US)

(73) Assignee: **Center for Neurologic Study**, La Jolla, CA (US)

(21) Appl. No.: **10/052,698**

(22) PCT Filed: **Sep. 22, 1994**

(86) PCT No.: **PCT/US94/10771**

§ 371 (c)(1),
(2), (4) Date: **Sep. 19, 1996**

(87) PCT Pub. No.: **WO96/09044**

PCT Pub. Date: **Mar. 28, 1996**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,863,927**
Issued: **Jan. 26, 1999**
Appl. No.: **08/464,792**
Filed: **Sep. 19, 1996**

(51) **Int. Cl.**[7] **A61K 31/44**; A61K 31/265; A61K 31/135

(52) **U.S. Cl.** **514/289**; 514/305; 514/491; 514/649; 514/651; 514/652; 514/654

(58) **Field of Search** 514/289, 305, 514/491, 649, 651, 652, 654

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,316,888	A *	2/1982	Nelson	424/127
5,166,207	A *	11/1992	Smith	514/270
5,206,248	A *	4/1993	Smith	514/289
5,350,756	A *	9/1994	Smith	514/289
5,352,683	A *	10/1994	Mayer et al.	514/289
5,366,980	A *	11/1994	Smith	514/289
5,502,058	A *	3/1996	Mayer et al.	514/289

OTHER PUBLICATIONS

Dickenson, A.H., "A cure for wind up: NMDA receptor antagonist as potential analgesics," *Trends in Pharm. Sci., 11*:307–309 (1990).*

Dickenson, A.H., et al., "Dextromethorphan and levorphanol on dorsal horn nociceptive neurones in the rat," *Neuropharmacology, 30*: 1303–1308 (1991).*

France, C. P., et al., "Analgesic Effects of Phencyclidine–Like Drugs in Rhesus Monkeys," *J. Pharmacol. Exp. Therapeutics, 250*: 197–201 (1989).*

Mao, J., et al., "Intrathecal treatment with dextrorphan or ketamine potently reduces pain–related behaviors in a rat model of peripheral mononeuropathy," *Brain Research, 605*: 164–168 (1993).*

McCarthy, J.P., "Some less familiar drugs of above," *Med. J. Australia 1971 (2)*: 1078–1081 (1971).*

McQuay, H. J., et al., "Dextromethorphan for the treatment of neurophatic pain: a double–blind randomised controlled crossover trial with integral n–of–1 deisgn," *Pain, 59*: 127–133 (1994).*

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Zhang et al. "Dextromethorphan: Enhancing its Systemic Availablity by Way of Low–dose QWuinidine–mediated Inhibition of Cytochrome P45O2D6," *Clin. Pharm. ? Ther.*, 51(6) :647–655 (1992).*

* cited by examiner

Primary Examiner—Phyllis G. Spivack

(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

Methods are disclosed for increasing the effectiveness of dextromethorphan in treating chronic or intractable pain, for treating tinnitus and for treating sexual dysfunction comprising administering dextromethorphan in combination with a therapeutically effective dosage of a debrisoquin hydroxylase inhibitor. A preferred combination is dextromethorphan and the oxidative inhibitor quinidine.

22 Claims, 1 Drawing Sheet

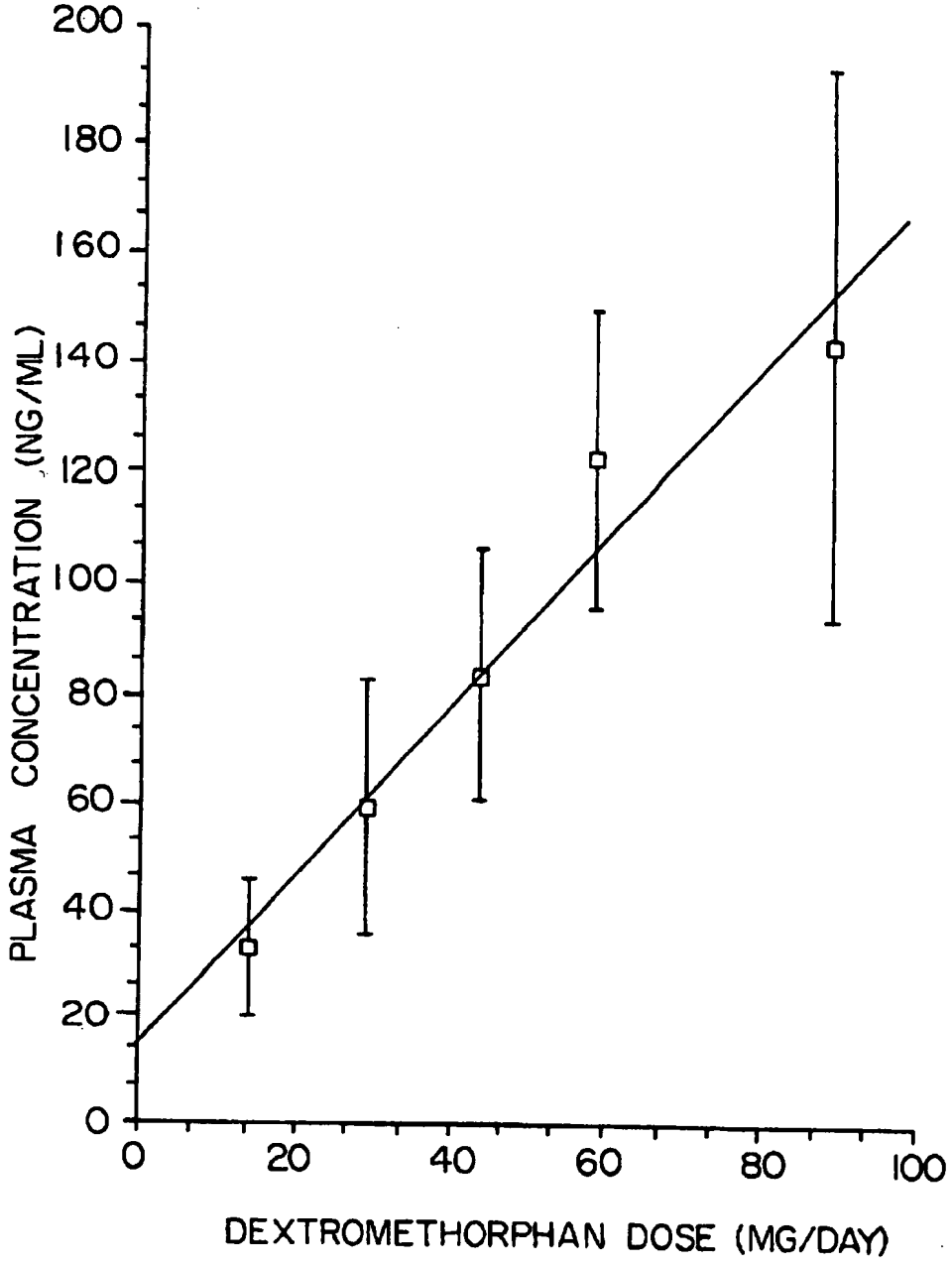
200
180
160
140
120
100
80
60
40
20
0
PLASMA CONCENTRATION (NG/ML)
0
20
40
60
80
100
DEXTROMETHORPHAN DOSE (MG/DAY)

FIG. 1

DEXTROMETHORPHAN AND AN OXIDASE INHIBITOR FOR TREATING INTRACTABLE CONDITIONS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

[This application is a 371 of PCT/US94/10771, filed Sep. 22, 1994.] *This application is the 35 U.S.C. §371 national stage application of PCT application No. PCT/US94/10771 filed Sep. 22, 1994, which is a continuation-in-part of application Ser. No. 08/114,845 filed Sep. 2, 1993, issued as U.S. Pat. No. 5,366,980 on Nov. 22, 1994, which is a continuation-in-part of application Ser. No. 07/896,053 filed Jun. 9, 1992, now abandoned.*

BACKGROUND OF THE INVENTION

This invention relates to pharmacology. More specifically, the invention relates to compositions of matter useful for preparing medicaments for the treatment of various disorders.

A number of chronic disorders have symptoms which are known to be very difficult to treat, and often fail to respond to safe, non-addictive, and non-steroid medications. Such disorders, such as intractable coughing, fail to respond to conventional medicines and must be treated by such drugs as codeine, morphine, or the anti-inflammatory steroid prednisone. These drugs are unacceptable for long-term treatment due to dangerous side-effects, long-term risks to the patient's health, or the danger of addiction. Other disorders, such as dermatitis, have no satisfactory treatment for the severe itching and rash at this time. Drugs such as prednisone and even tricyclic antidepressants, as well as topical applications, have been tried, but do not appear to offer substantial and consistent relief.

Chronic pain due to conditions such as stroke, cancer, trauma, as well as neuropathic pain resulting from conditions such as diabetes and shingles (herpes zoster), for example, is also a problem which resists treatment. Chronic pain is estimated to affect millions of people. A variety of therapies for this type of pain have been tried, but there remains a need for safe and effective treatments.

The compound dextromethorphan, or (+)-3-methoxy-N-methylmorphinan, has been used as a cough suppressant ingredient in cough syrups. Dextromethorphan has also been tested as a potential therapeutic agent for stroke, and progressive neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis. However, the effectiveness of dextromethorphan for the treatment of any disorder has been limited because it is rapidly broken down by the liver and excreted in most individuals.

It is an object of the present invention to provide a combination of compounds useful for the preparation of medicaments which will effectively treat formerly intractable conditions not responsive to other medications. It is also an object of the present invention to provide medicaments which are safe, non-addictive, and relatively free of side-effects for patients suffering from long-term intractable conditions.

SUMMARY OF THE INVENTION

The present invention provides compounds which are useful in the preparation of medicaments for the treatment of a variety of disorders including intractable coughing, dermatitis, chronic pain, tinnitus and sexual dysfunction. These compounds are a therapeutically effective dosage of dextromethorphan and a therapeutically effective dosage of a second agent, an inhibitor of enzymatic dextromethorphan oxidation. This combination of compounds can be administered together, or individually. A preferred combination is dextromethorphan and the oxidative inhibitor quinidine. Inhibitors which may also be used include quinine, yohimbine, fluoxetine, haloperidol, ajmaline, lobeline, and pipamperone.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the relationship between DM oral dosages and DM plasma concentrations in patients receiving 150 mg/day of quinidine orally.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

As used herein the term dextromethorphan (hereinafter, DM) refers to (+)-3-methoxy-N-methylmorphinan, or therapeutically effective salts and analogs thereof.

As used herein the term "antioxidants" or "oxidative inhibitors" refers to inhibitors capable of inhibiting the oxidation of DM by the liver enzyme debrisoquin hydroxylase.

As used herein, the term "intractable" or "refractory" coughing refers to coughing that will not respond adequately to non-addictive, non-steroid medications.

As used herein, the term "dermatitis" or "eczema" refers to a skin condition which includes visible skin lesions which may be accompanied by an itching or burning sensation on the skin. This condition does not readily respond to non-prescription drugs, lotions, or ointments.

As used herein the term "chronic pain" refers to long-term pain resulting from conditions such as stroke, cancer and trauma, as well as neuropathic pain due to deterioration of nerve tissue such as postherpetic neuralgia (PHN) resulting from herpes zoster infection, and diabetic neuropathy resulting from long-time diabetes.

As used herein the term "tinnitus" refers to a syndrome characterized by a high-pitched ringing in the ears thought to be induced by loss of motility of the outer hair cells of the cochlea of the ear.

The present invention provides compositions for use in the preparation of medicaments for the effective treatment of a variety of chronic and intractable disorders which failed to respond to other treatments. These compositions are a therapeutically effective dosage of dextromethorphan (DM), or a pharmaceutically acceptable salt or analog thereof, in combination with a therapeutically effective dosage of an inhibitor of enzymatic dextromethorphan oxidation by the liver enzyme debrisoquin hydroxylase. The chronic and intractable disorders which have responded to medicaments containing a dextromethorphan/antioxidant combination include intractable coughing, dermatitis, chronic pain and tinnitus. Relatively potent antioxidants include quinidine and quinine. Other antioxidants which are milder include yohimbine, fluoxetine, haloperidol, ajmaline, lobeline, pipamperone.

It has been found that the use of quinidine and other oxidation inhibitors when administered in conjunction with DM has pronounced effect in increasing and stabilizing the quantity of DM circulating in the blood of a patient. This effect is discussed in U.S. Pat. No. 5,166,207 to Smith, issued Nov. 24, 1992, and in Zhang, Y., Clin. Pharmacol. Ther. 51: 647–655 (1992), both of which are herein incorporated by reference.

Dextromethorphan (hereinafter DM) is the common name for (+)-3-methoxy-N-methylmorphinan. This compound is described in detail in Rodd et al., Chemistry of Carbon Compounds, Elsevier Publ., New York (1960), for example, which is herein incorporated by reference. DM is a non-addictive opioid having a dextrorotatory enantiomer (mirror image) of the morphinan ring structure which forms the molecular core of most opiates.

DM has been used as an ingredient of cough suppressant in over-the-counter cough syrup. The cough-suppressing activity of DM is thought to be due primarily to its actions as an agonist on a class of neuronal receptors known as sigma receptors or high-affinity dextromethorphan receptors. Although these receptors are sometimes referred to as sigma opiate receptors, it is not clear whether they are in fact opiate receptors. Sigma receptors are inhibitory receptors and the activation of these receptors by DM or other sigma agonists causes the suppression of certain types of nerve signals. Dextroinethorphan is also thought to act on another class of receptors known as N-methyl-D-aspartate (NDMA) receptors, which are one type of excitatory amino acid (EAA) receptor. Unlike its agonist activity at sigma receptors, DM acts as an antagonist at NMDA receptors, suppressing the transmission of nerve impulses mediated through NMDA receptors. Since NMDA receptors are excitatory receptors, the action of DM as an NMDA antagonist also results in the suppression of nerve signals. In addition, DM has been reported to suppress activity at neuronal calcium channels. It is the antagonist activity of DM at NMDA receptors which is through to be one of the common links between some of the various conditions which respond to medicaments containing a DM/antioxidant combination.

When used in therapeutic applications, DM disappears rapidly from the bloodstream of most individuals, as described in Dayer et al., Clin. Pharmacol. Ther. 56:34–30 (1989), Vetticaden et al., Pharmaceut. Res. 6:13–19 (1989), and Ramachander et al., J. Pharm. Sci. 66: 1047–1049 (1977), which are herein incorporated by reference. DM is broken down in the liver into several metabolites. DM can be oxidized by O-dimethylation, in which one of the methyl groups is removed and two metabolites, dextrorphan and 3-methoxymorphinan, are produced. If the second methyl group is removed, the resulting metabolite is 5-hydroxymorphinan. Dextrorphan is known to have many of the biological activities of DM. However, dextrorphan and 5-hydroxymorphinan become covalently bonded to other compounds in the liver, primarily glutathione to form glucuronide or sulfate conjugates, which can not readily cross the blood-brain barrier and which are quickly eliminated from the body in the urine.

The particular enzyme primarily responsible for DM oxidation is debrisoquin hydroxylase, also known as sparteine monooxygenase, and also referred to in the literature variously as cytochrome P-450$_{DB}$, as cytochrome P-450db1 (or db1), and as cytochrome P-4502D6. Hereinafter, this enzyme is referred to as debrisoquin hydroxylase. Debrisoquin hydroxylase belongs to the family "cytochrome P-450" enzymes, or as "cytochrome oxidase" enzymes. These enzymes typically found in high concentrations in liver cells primarily in liver microsomes, and in lower concentrations in various other organs and tissues such as the lungs. By oxidizing lipophilic compounds, cytochrome oxidase enzymes eliminate compounds from the body that might otherwise act as toxins or accumulate to undesired levels. Typically, oxidation renders lipophilic compounds more soluble in water and therefore, more easily eliminated in the urine or in aerosols exhaled out of the lungs. The debrisoquin hydroxylase enzyme apparently is also present in brain tissue (Fonne-Pfister et al., Biochem. Biophys. Res. Communic. 148: 1144–1150 (1987), Niznik et al., Arch. Biochem. Biophys. 26:424–432 (1990), Tyndate et al., Mol. Pharmacol. 40:63–68 (1991)), although its function in the brain is not fully understood.

Dextromethorphan is widely available over-the-counter in cough syrups, at dosages up to about 120 mg/day for an adult. This invention anticipates DM dosages in the range of about 20 mg/day to about 200 mg/day, preferably in the range of 20 to 150 mg/day, depending on factors such as the weight of the patient, the severity of the disorder, and the potency and dosage of the antioxidant agent used in conjunction with DM.

Quinidine is a dextrorotatory steroisomer of quinine. Quinidine is commonly used to treat cardiac arrhythmias, and is considered a relatively strong cardiac medicine. Quinidine is commercially available from a number of sources, for example, A H. Robins, Richmond, Va., but is available to the public only with a doctor's prescription. Both DM and quinidine are commercially available in powder form, and capsules of a specific dosage can be prepared as desired by commercial vendors. The dosage of quinidine which was found to provide a major increase in DM concentration in the blood of most patients was equal to or less than 150 mg/day, depending on the individual. The present invention contemplates dosages ranging from 50 mg/day to 300 mg/day, preferably from 50 mg/day to 150 mg/day. In some patients a dosage of about 50 mg/day is found to be effective. In contrast the dosage used for anti-arrhythmic control in cardiac patients is between 600–1200 mg/day.

A number of antioxidants other than quinidine have already been identified in the literature, using in vitro screening. These are reported in Inaba et al., Drug Metabolism and Disposition 13:443–447 (1985), Fonne-Pfister et al., Biochem. Pharmacol. 37:3829–3835 (1988) and Broly et al., Biochem. Pharmacol. 39:1045–1053 (1990), all of which are herein incorporated by reference. As reported in Inaba et al., agents with a K_i value (Michaelis-Menton inhibition values) of 50 micromolar or lower include nortriptyline, chlorpromazine, domperidone, haloperidol, pipamperone, labetalol, metaprolol, oxprenolol, propranolol, timolol, mexiletine, quinine, diphenhydramine, ajmaline, lobeline, papaverine, and yohimbine. Preferred compounds having particularly potent inhibitory activities include yohimbine, haloperidol, ajmaline, lobeline, and pipamperone, which have K_i values ranged from 4 to 0.33 μM. In comparison, the K_i value of quinidine is 0.06 μM. of these inhibitors quinine sulfate, disulfiram, cimetidine, fluoxetine, propranolol, and nortriptyline were tested for the ability to stabilize the concentration of DM in the blood stream, as described in detail in Example 4 below. As expected, the results of these studies show an increase in levels of DM which is not as pronounced as that when DM is co-administered with quinidine. In addition, the results indicated substantial variations between individuals in the effect of each antioxidant. Quinine, having a structure similar to quinidine, was shown to be effective in increasing DM/DRP ratios in the individuals tested. Other drugs showed more variability among individuals. This variability indicates that individual antioxidants would be pre-tested using the methodology described in Example 4 below, before using on patients. It should also be noted that a number of antioxidants have their own pharmaceutical effects, which vary widely, and which would be taken into consideration by a prescribing physician. Dosages of other antioxidants will vary with the

antioxidant, and should be determined on an individual basis using the protocal described in Example 4.

In addition to the antioxidants reported above, it has also been found that fluoxetine, sold by Eli Lilly and Co. under the trade name Prozac, is effective in increasing DM concentrations in the blood of some people. For example, a single patient who was taking 20 mg fluoxetine twice a day registered a blood level of 40 ng/ml of DM when administered DM according to the testing outlined in Example 4.

The optimal dosage of both dextromethorphan and any of the antioxidant to be administered to specific patient can be determined by administering various dosages of each drug and then (1) analyzing blood samples to determine the concentration of DM in the circulating blood, and/or (2) evaluating the patient's progress to determine which combination of dosages provides the best result in effectively suppress the symptoms being targeted.

A number of factors influence the dosage of DM and antioxidant which would be appropriate for a particular individual. One very important factor is the individual's ability to metabolize DM. It is known that a substantial fraction of the general public, estimated from 7 to 10%, do not have a properly functioning gene encoding the debrisoquin hydroxylase enzyme. These persons are referred to by doctors and pharmacologists as "poor metabolizers", while those having the gene encoding debrisoquin hydroxylase are known as "extensive metabolizers". "Poor metabolizers" are regarded as somewhat high-risk patients who must be treated with special care and attention, since they are overly sensitive to certain drugs that can be prescribed safely to people who have the full set of cytochrome P450 enzymes.

In addition to the inhibition of debrisoquin hydroxylase, other cytochrome P450 isozymes are also likely to be suppressed by quinidine or other inhibitors, with varying levels of binding affinity. This is described in articles such as Kupfer et al., Lancet ii:517–518 (1984) and Guttendorf et al., Ther. Drug. Monit. 10:490–498 (1988), which are herein incorporated by reference. In addition, cytochrome P-450 enzymes are non-specific to the extent that a single isozyme can react with numerous substrates having widely different chemical structures, and various isozymes are known to have overlapping activity on a single substrate. Accordingly, even though quinidine exerts its most marked effect on debrisoquin hydroxylase, it may suppress a number of other cytochrome P450 enzymes as well, thereby subjecting a patient to a more general loss of normal and desirable liver activity.

Since DM is considered to be a safe drug which is readily available as an over-the-counter medication, it can be used as a convenient tool or probe drug for determining whether a patient is a extensive metabolizer or a poor metabolizer. Such diagnostic tests are performed so that a patient who is a "poor metabolizer" can be identified and protected against various drugs which he or she cannot metabolize properly. However, if a patient is taking a drug such as quinidine, the level of enzymes will be inhibited, and the diagnostic test for identifying "poor metabolizers" will not be accurate, and will reflect the presence of the inhibitor.

In addition, DM may cause side effects in some people such as diarrhea, drowsiness, lightheadedness, or loss of appetite, and in some cases, impotence in male patients. The likelihood and severity of such side-effects will be increased by antioxidants, in direct proportion to the potency of the antioxidant used. Therefore, the DM-quinidine combination or DM-antioxidant combinations disclosed herein is currently anticipated for use only under the supervision of a physician, who would determine the appropriateness of the treatment. All the appropriate precautions should be taken with the use of any antioxidant, as would be appreciated by a physician and others of skill in the art. However, the dosage of quinidine that provides a substantial increase in DM concentration in the blood is only a fraction of the dosages normally used for anti-arrhythmic action.

For some patients, combinations of DM and antioxidants other than quinidine are preferred for preparing medicaments. In some instances, individual may not tolerate quinidine or quinidine-DM combinations, for example, when a patient may be allergic to quinidine, or if a patient is suffering from a heart condition known as a prolonged QT interval, and therefore cannot tolerate quinidine. Less potent oxidation inhibitors are also preferred in combination with DM for example, as a second agent that can be alternated with quinidine to avoid developing a tolerance that would require increasing dosages of quinidine; or for patients who have a moderate condition such as coughing that will not respond adequately to other treatments, but which is not severe enough to require a potent enzyme inhibitor.

It was unexpectedly discovered that DM in conjunction with quinidine was highly effective in reducing the symptoms of "emotional lability". Emotional lability is a complex problem in which patients suffering from bilateral neurological damage typically due to a stroke or head injury or a neurologic disease such as ALS or Alzheimer's disease are unable to control spasmodic emotional outbursts such as explosive laughing or uncontrollable weeping. In patients suffering from brain damage leading to emotional lability, such outbursts often occur at very inappropriate times and without provocation. The ability of DM in conjunction with quinidine to control emotional lability is described in U.S. Pat. No. 5,206,248, issued on Apr. 27, 1993, which is herein incorporated by reference. This effect of DM-quinidine in controlling emotional lability was not observed in any patients who received DM alone.

It has now been found that the combination of compounds described above are extremely effective in medicaments for the treatment for other chronic disorders which do not respond well to other treatments. A DM/antioxidant combination can be used to effectively treat severe or intractable coughing, which has not responded adequately to non-addictive, non-steroid medications. Intractable coughing is a consequence of respiratory infections, asthma, emphysema, and other conditions affecting the pulmonary system.

Tests using a DM-quinidine combination to treat intractable coughing in human patients is described in Example 5 below. In all patients tested, treatment with a combination of DM and an antioxidant provided highly beneficial results with minimal side-effects. These results clearly confirmed the effectiveness and utility of the use of DM-antioxidant in preparing medicaments for treatment of intractable coughing.

This invention also discloses the use of DM in combination with an antioxidant in preparing medicaments for treating dermatitis. As used herein, "dermatitis" or "eczema" is a skin condition characterized by visible skin lesions and/or an itching or burning sensation on the skin. The effectiveness of the DM-quinidine combination for treating dermatitis was first observed as an unexpected beneficial side effect during testing on an ALS patient who happened to suffer from severe dermatitis. This drug combination showed a beneficial effect on dermatitis when subsequently tested by a dermatologic specialist on a non-ALS patient suffering from severe dermatitis. After these initial results, an additional study was conducted on several patients suffering from dermatitis, by administering DM-quinidine cap-

sules orally. The results showed marked relief from the rash and itching. Topical administration of DM or DM-antioxidant containing medicaments is contemplated for person suffering from dermatitis. These results are described in more detail in Example 6.

It is also contemplated that DM alone can be effective in treating dermatitis for certain patients who are classified as "poor metabolizers" due to a genetic inability to express functional copies of the debrisoquin hydroxylase enzyme. For these individuals DM alone, at safe dosages, will be sufficient to treat the dermatitis effectively without requiring concomitant use of an antioxidant to increase DM levels in the blood.

The present invention also provides for the use of DM and an antioxidant in medicaments for the treatment of chronic pains from conditions such as stroke, trauma, cancer, and pain due to neuropathies such as herpes zoster infections, and diabetes.

Neuropathic pain includes postherpetic neuralgia, and diabetic neuropathy. Postherpetic neuralgia (PHN) is a complication of shingles and occurs in approximately 10 percent of patients with herpes zoster. The incidence of PHN increases with age. Diabetic neuropathy is a common complication of diabetes which increases with the duration of the disease. The pain for these types of neuropathies can be described as the following: burning steady pain often punctuated with stabbing pains, pins and needles pain, or toothache-like pain. The skin can be sensitive with dysesthetic sensations to even light tough and clothing. The pain can be exacerbated by activity, temperature change or emotional upset. The pain can be so severe as to preclude daily activities or result in sleep disturbance or anorexia. The mechanisms involving in producing pain of these types are not well understood, but may involve degeneration of myelinated nerve fibers. It is known that in diabetic neuropathy both small and large nerve fibers deteriorate and therefore the thresholds for tolerance of thermal sensitivity, pain, and vibration are reduced over time. Dysfunction of both large and small fiber functions is more severe in the lower limbs when pain develops. Most of the physiological measurement of nerves that can be routinely done in patients experiencing neuropathic pain demonstrate a slowing of nerve conduction over time. To date, treatment for neuropathic pain has been less than universally successful.

Human patients suffering from chronic pain due to stroke, diabetes, and other causes, were placed on a dosage of DM-quinidine taken orally. All patients experienced some degree of pain relief after receiving DM-quinidine for two to four weeks. This study is described in Example 7 below.

It was noted that a side-effect suffered by some of the male patients in earlier emotionality studies and the dermatitis studies described in Example 7 included instances of impotence. This impotence persisted until the patient stopped taking medication containing DM-quinidine. Therefore, DM-antioxidants containing medicaments are contemplated for the treatment of sexual dysfunctions including priapism or premature ejaculation.

One of the patients involved in the pain studies also suffered from tinnitus, a syndrome characterized by a high pitched ringing in the ears. After treatment with DM/quinidine, the patient reported that the ringing had ceased. Therefore, based on this evidence and the involvement of NMDA receptors in the cochlear system, the use of DM/antioxidants in the preparation of medicaments for the treatment of tinnitus is also contemplated by the present invention.

The medicaments used for treating the various disorders described above are prepared from DM and an appropriate antioxidant, or alternatively from the salts and analogs of DM and the various antioxidants. The terms "salt" and "analog" are used in their conventional pharmaceutical sense, and are limited to pharmacologically acceptable and therapeutically effective salts and analogs of dextromethorphan or an antioxidant as discussed herein. The term "pharmacologically acceptable" embraces those characteristics which make a salt or analog suitable and practical for administration to humans; for example, such compounds must be sufficiently chemically stable under reasonable storage conditions to have an adequate shelf life, they must be physiologically acceptable when orally ingested, and they must not be addictive or cause unacceptable side effects. Acceptable salts can include alkali metal salts as well as salts of free acids or free bases. Acids that may be employed to form acid addition salts include inorganic acids such as sulfate or chloride salts, as well as organic acids. Alkali metal salts or alkaline earth metal salts might include, for example, sodium, potassium, calcium or magnesium salts. All of these salts can be prepared by conventional means. Various salts of the compounds described herein which are currently in widespread pharmaceutical use are listed in sources well-known to those of skill in the art such as The Merck Index. The constituent used to make a salt of an active drug discussed herein is not critical, provided that it is non-toxic and does not substantially interfere with the desired activity.

A pharmaceutical analog refers to a molecule that resembles a referent compound but which has been modified to replace one or more moieties of the referent molecule with alternate moieties or other substituents that do not ionize and dissociate readily, as occurs in salts. For example, if a hydrogen or chloride moiety is replaced by a methyl group, the resulting molecule would be regarded as an analog. To be covered herein, the analog-producing substituent must not destroy the anti-tussive or anti-dermatitis or other activities of the referent molecule.

Administration of the medicaments to be prepared from the compounds described herein can be by any method capable of introducing the compounds into the bloodstream. Administration can be orally, or by parenteral, intravenous, or subcutaneous injection, for example, as well as by topical or inhalant formulations. In particular topical administration as lotions or ointments is contemplated to treat dermatitis. Likewise, inhalable aerosols are contemplated for treating intractable coughing. An injectable, topical, or inhalant formulation contains a mixture of active compounds with pharmaceutically acceptable carriers or diluents. Various other formulations for oral and injectable medicaments have been described in U.S. Pat. No. 5,166,207 to Smith, which is herein incorporated by reference.

EXAMPLES

The initial testing described in Examples 1 to 3 were preformed on patients having amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's disease). At the time it was thought that DM might have an effect in arresting the progression of ALS and other neurological disorders. Although the studies described in Examples 1 to 3 were done on patients suffering from ALS, most of whom are adults more than 40 years old, no differences were detected in the metabolism of DM in ALS patients, compared to reported findings involving adults who do not have ALS or to one-day tests involving healthy volunteers as a control population.

Example 1

Urinary DM/DR Ratios

Six patients suffering from ALS were administered orally a single 60 mg dextromethorphan dose. Several hours later,

a urine sample was collected, and the urine concentrations of dextromethorphan (DM) and dextrorphan (DR) were measured as described below to determine a DM/DR ratio. A low DM/DR ratio indicates that DM is being rapidly oxidized to the DR metabolite in that body of that patient. In a different week, 60 mg of DM and 150 mg of quinidine were orally administered to the same patients, and urinary DM and DR levels and DM/DR ratios were determined again.

DM and DR urinary levels without quinidine were determined by adding 40 mg of thebaine as an internal standard to 1 mL of urine. To this was added 2000 units of betaglucuronidase in 1 mL of acetate buffer (0.1M, pH 5.0). The mixture was incubated for 18 hours at 37° C. and then extracted by adding 1 mL of phosphate buffer (pH 12, 0.10M) and 7 mL of n-butanol/hexane (10:90 v/v). After mixing and centrifugation, the organic layer was transferred to a clean tube, acidified with 400 uL of 0.01N HCL and 20 microliters (uL) of aqueous phase injected into a high performance liquid chromatography (HPLC) system. The HPLC used a phenyl column equilibrated with a mobile phase of acetonitrile:water (51:49 v/v) containing 10 mM $KHPO_4$, 10 mM hexane sulfonic acid, pH 4.0 (flow rate 1.2 mL/min). Detection of thebaine, dextromethorphan and dextrorphan was achieved by fluorescence (Kratos FS-980 Fluorometer) with an excitation wavelength of 228 nm and no emission cutoff filter.

A gas chromatograph/mass spectroscopy (gc/ms) assay was employed for determining dextromethorphan and dextrorphan levels in the presence of quinidine. Briefly, 0.5 ml urine samples were spiked with 500 nanograms (ng) of dimethacrine. The urine pH was adjusted to 0.5 with 0.1M acetate buffer (usually about 1.0 ml), and beta-glucuronidase was added (2000 units/ml urine). The mixture was incubated and shaken at 37° C. for 18 hours. The urine was subsequently adjusted to pH 10–11 with 1.0 mL of phosphate buffer and the urine extracted with 5 mL of dichloromethane. The dichloromethane extract was evaporated under nitrogen, reconstituted in 300 uL of BSTFA and injected onto a gc/ms analyzer equipped with a capillary SE-30 column. Gas chromatographic conditions were: injector and transfer line temperature 250° C., oven 70° C. to 260° C. at 20° C. per minute, and source temperature 180° C. Detection was by selected ion monitoring at m/z 271 for dextromethorphan, 294 for the internal standard, and 329 for dextrorphan. Typical standard curves for dextromethorphan and dextrorphan were provided. Assay sensitivity was 100 ng/ml for dextromethorphan and 400 ng/ml for dextrorphan.

The results, in Table 1, indicate that quinidine is a potent inhibitor of dextromethorphan metabolism. The DM/DR ratio in all test subjects was increased by at least 2 and usually more than 3 orders of magnitude.

TABLE 1

URINGARY DM/DR RATIOS

Patient # #	DM/DR Ratio, no quinidine	DM/DR Ratio, 150 mg quinidine
1	0.0048	4.090
2	0.0220	3.460
3	0.0002	0.635
4	0.0003	0.420
5		0.631
6	0.054	3.29

Follow up tests were done on more than 50 people, including ALS patients and healthy controls who volunteered for one-day tests. The ALS patients received DM and quinidine on a daily basis over several weeks, while control subjects received only a single dose of each drug. The results were very similar to the data contained in Table 1.

Example 2

Plasma Concentrations of DM

Five patients were orally administered 120 mg of DM, with no co-administration of quinidine. Between 10 and 12 hours later, blood was sampled, blood plasma was isolated by centrifugation, and the plasma was analyzed to determine the DM concentration using the thebaine/HPLC method.

During a different week, the same patients were orally administered 60 mg of DM (half the control dosage) and 150 mg of quinidine. Between 10 and 12 hours later, blood was sampled and the plasma was analyzed for DM using thebaine/HPLC.

The results, in Table 2, indicate that quinidine causes a major increase in the concentration of DM in the blood plasma.

TABLE 2

Effects of 150 mg/day quinidine on plasma dextromethorphan levels

PATIENT	DEXTRO-METHORPHAN DOSE	DEXTRO-METHORPHAN PLASMA LEVEL	QUINIDINE DOSE (MG/DAY)
1	120 MG/DAY	NOT DETECTABLE	0
	60 MG ONCE	33 NG/ML	150
2	120 MG/DAY	9.3 NG/ML	0
	60 MG ONCE	29.7 NG/ML	150
3	120 MG/DAY	NOT DETECTABLE	0
	60 MG ONCE	29.0 NG/ML	150
4	120 MG/DAY	16.5 NG/ML	0
	60 MG ONCE	28.8 NG/ML	150
5	120 MG/DAY	6.05 NG/ML	0
	60 MG ONCE	45.6 NG/ML	150

Subsequently, plasma levels were determined for about 15 other ALS patients who received dextromethorphan and quinidine over a prolonged period of time. The results were very similar to the data in Table 2.

Example 3

Dose-Response Study

Additional studies were undertaken using a range of dosages of DM to establish a dose-response curve that correlates with plasma concentrations 10 to 12 hours later (determined as described in Example 2). All patients received 150 mg of quinidine daily. The results of those studies are shown in graphical form in FIG. 1, with mean values shown as open squares and standard deviation ranges shown by vertical bars. The ascending line through the median values is a linear approximation; a curve based on more extensive data would probably show a horizontal asymptote.

The results of the tests described in the foregoing Examples indicate that if quinidine is co-administered with DM, then DM circulation in the blood is increased and prolonged, without causing severe side effects. Accordingly, the co-administration of an antioxidant compound such as quinidine in conjunction with DM can increase the effectiveness of DM in any context that depends upon the concentration of DM circulating in the blood.

Example 4

Use of Other Antioxidants

Since some patients cannot tolerate quinidine well, the ability of several other candidate antioxidants to inhibit DM

oxidation in various people were tested. In these tests, DM was administered at a constant dosage to various individuals, all were healthy volunteers. DM was taken both before and after a candidate antioxidant was taken, and urine samples were collected at appropriate times and analyzed to determine the quantity of DM and its principle metabolite dextrorphan (DRP) in the urine. A DM/DRP ratio of zero indicated that substantially all of the DM had metabolized into DRP in that patient. A ratio higher than zero indicated that the DM had not been completely metabolized, and a significant quantity of DM remained in the urine.

Twelve healthy volunteers were studied. A first urine sample was taken after initial DM administration, before any antioxidant was administered, to determine a baseline value for that person, and all volunteers were confirmed to be "extensive metabolizers" with baseline DM/DRP ratios or 0.06 or less, except for one "poor metabolizer" with a DM/DRP ratio of 1.338, used to provide a control. Urine samples were analyzed using high performance liquid chromatography (HPLC) to quantitatively evaluate the areas contained within the chromatography peaks displayed by DM and its principle oxidized metabolite (dextrorphan, DRP). A DM/DRP ratio higher than zero indicated that the DM was not completely metabolized and that a significant quantity of DM is present in the urine of the patient; a ratio of 0 indicates that substantially all of the DM was metabolized into DRP.

After the baseline DM/DRP value for each volunteer had been determined, a candidate antioxidant was administered. These agents included quinine sulfate, disulfiram, cimetidine, fluoxetine, propranolol, and nortriptyline. After an appropriate delay, a second urine sample was obtained and analyzed. Each agent was administered to two patients.

The most potent results observed in these tests were from quinamm (quinine sulfate). In one subject, the DM/DRP ration increased from 0.02 (pre-quinine baseline) to 0.09; in the other subject, the DM/DRP ration increased from 0.00 to 0.05. When the other candidate agents were tested, the results indicated high levels of variability between different individuals. For example, in the two subjects who took fluoxetine, the DM/DRP ratio for one increased from 0.00 (pre-drug baseline) to 0.11, while in the other, the ratio decreased from 0.03 to 0.00. In the two subjects who took propranolol, the DM/DRP ratio increased from 0.00 to 0.02 in one, while in the other it decreased from 0.02 to 0.00. In the two subjects who took disulfiram, the DM/DRP ratio increased from 0.06 to 0.08 in one, while it decreased from 0.06 to 0.00 in other. These levels of variability were not surprising, since it is well known that different people have important variations in their oxidative enzymes.

Example 5

Tests On Patients With Intractable Coughing

Three patients were tested under a doctor's supervision, all of whom had been suffering from intractable coughing that had persisted for months. One patient was previously treated with prednisone, an anti-inflammatory steroid, which has adverse long-term side effects. A second patient had coughed for 8 months following a respiratory infection, and would only respond temporarily to cough syrup containing codeine, which is addictive and cannot be taken for long periods. A third patient had such severe coughing following a respiratory infection that he suffered several broken several ribs. Antibiotics for a respiratory infection and anti-inflammatory inhalant drugs were prescribed for a suspected asthmatic condition.

The initial tests on three patients with intractable coughing indicated highly effective results, with virtually no side effects.

Patient EAR, a 70 year old female, had suffered from a recurrent persistent non-productive cough for several years. This cough would respond to prednisone administration, but it would return shortly after the prednisone was discontinued, and continuous medication with prednisone was deemed to be unacceptable. She had tried various cough syrups, with little benefit, and her cough had not responded well to albuteral (a beta-adrenergic bronchodilator) or ipratropium bromide (an anticholinergic bronchodilator); both were administered using a nebulizer-type inhaler. When she was given 1 capsule per day of 75 mg quinidine and 60 mg DM, the cough initially stopped but returned after several days. When the dosage was increased to 2 capsules/day, the cough stopped and did not return. She reported no side effects.

Patient SP, a 38 year old male nonsmoker with no history of asthma, had suffered for about 8 months from a persistent non-productive cough. It receded temporarily when he was given penicillin and a cough syrup with codeine, but it returned after he stopped taking codeine. When he began taking 1 capsule per day of 75 mg quinidine and 60 mg DM, and after a few days, the cough stopped almost completely, and he coughed only rarely during the day. He reported no side effects.

Patient RC, a 43 year old male nonsmoker with no history of asthma, suffered for about 5 months from a cough, which initially began with an upper respiratory viral infection followed by a bacterial infection. The coughing became so severe that it led to fractured ribs. When he first sought medical attention, the cough produced yellow phlegm. The phlegm was cleared up by antibiotics but the cough persisted despite inhalation treatment for a suspected asthma condition with flunisolide (an anti-inflammatory steroid) and inhalation treatment with albuterol. The cough did not substantially improve when the patient took only 1 capsule/day, but when he began taking 2 capsules/day, it improved by roughly 90% within a few days. Although he occasionally coughed, his condition improved so much that he sometimes forgot to take his medication. He reported no side effects.

In all cases, the patients were delighted with the results. The combined DM-antioxidant treatment was very effective in almost completely eliminating coughing that could not be treated adequately by any other medications, and the DM-antioxidant treatment caused minimum reported side effects. The results clearly confirm the effectiveness and utility of the invention.

Example 6

Treatment of Dermatitis

During an initial examination, it was discovered that patient BT, a Caucasian female in her 60's who was suffering from ALS, suffered from a severe dermatologic condition involving lesions which appear in small patches. Her condition had been diagnosed as atopic dermatitis. The etiology is unknown. The patient reported that the lesions were severely itchy, and she had been suffering from it for roughly ten years. She had been prescribed a number of drugs (including various steroids such as prednisone) in an effort to control the itching; the most recent prescription was "Doxepin," a tricyclic antidepressant. None of those agents offered much relief.

The patient began an initial treatment of quinidine alone (150 mg/day) for a week. After it had been established that

she did not have an adverse reaction, she began to receive DM as well, beginning at 30 mg/day, and increasing after 1 month to 120 mg/day.

During the second monthly visit after beginning the DM/quinidine treatment, it was found that the patient had obtained an almost total cessation of any itching sensations, with partial resolution of her lesions. A follow-up exam some weeks later indicated that the patient's skin lesions had completely healed with no apparent evidence of scar tissue.

After seeing this result, additional tests were performed by a dermatologic specialist at a nearby university. The first test by the specialist involved a male Caucasian who suffered from severe but intermittent dermatitis. The relapse resolved in less than two weeks after starting treatment. Due to the intermittent nature of the patient's dermatitis, this result could not be conclusively attributed to the DM-antioxidant combination; nevertheless, the disappearance of the relapse promptly after DM-antioxidant treatment began strongly suggested that the DM-antioxidant combination probably had a substantial beneficial effect.

After the initial successes described above, additional studies to determine the effectiveness of DM/quinidine for treating dermatitis were carried out as follows. Patients suffering from dermatitis were first evaluated as to general physical condition, and also evaluated by the physician using a "standardized disease activity scoring" or "lesion score" for the severity of the dermatitis condition. The standardized disease activity score or lesion score is completed by the examining physician who scores on a severity scale of 1 to 5 for both erythema and surface damage for a given area (1 to 5 in size) on the patient's body. The total score was then calculated. The patient indicated on a subjective visual scale the severity of itching and rash due to dermatitis. DM/quinidine were taken in capsule form of 30 mg DM and 75 mg quinidine per capsule. The patient was usually re-examined in two weeks, and then again six weeks or more after the initial exam and receiving the DM/quinidine capsules.

Patient #1 was a 40 year old female patient who suffered from atopic eczema since birth, which flares up with stress. The patient was initially evaluated using the standardized disease activity scoring system and filling out the subjective itching/rash analysis forms. The initial score was 42. The patient indicated the initial itching score as severe, and rash as severe to moderate.

The patient reported side effects of nausea and headache as side effects, and stopped the drugs after five days. She was then placed on a reduced dosage of 30 mg/25 mg DM/quinidine per day. Subsequently, the patent reported the rash and itching almost totally cleared within five days. The two week evaluation showed the patients' total standardized disease activity score was reduced dramatically to 13. The patient's face in particular was strikingly improved. At two weeks, the patient reported the itching reduced to moderate to slight and the rash reduced to moderate to slight. Four weeks later, the patient reported continued headache side effects even when on a reduced dosage. However, the total standardized disease activity score remained lower than initially with a total score of 24. She reported itching in the severe to moderate range, and rash in the moderate range.

Patient #2 was a fifty five year old male with a 20 year history of chronic eczema. The rash was located mainly on the thighs. The initial total standardized disease activity score was initially 12. The patient received a 30 mg/75 mg dosage of DM/quinidine once a day for 5 days, then every 12 hours for the duration. The patient initially reported severe itching and moderate rash. After about 1 month the lesion score remained at 12, but the patient reported itching was reduced to the low moderate range and the rash was reduced to the moderate to slight range. The medications were eventually discontinued due to side effects.

Patient #3 was a fifty four year old male who began suffering from eczema seven or eight years ago. The initial physical exam showed fairly generalized excoriated eczematory dermatitis, which was especially severe on his lower legs. The rash was prone to a secondary infection. The initial lesion score was 112. The patient initially rated his itching as moderate and rash as low moderate. The patient received a 30 mg DM/75 mg quinidine capsule once a day for five days, then every 12 hours for the duration.

After two and a half months, the patient was again evaluated, and received a lesion score of 90. The overall appearance was reported to be improved, and the rash less red. However, the patient reported the same degree of itching and rashes. The patient reported some side effects, most of which disappeared after a few days. However, the patient reported a delay in reaching orgasm, a side-effect which persisted as long as the medications were continued.

Due to the reports of side effects in some patients, the application of DM/quinidine as a topical cream is considered for the treatment of dermatitis.

Example 7

Treatment of Pain

The following pain studies were undertaken to determine if the dextromethorphan/quinidine composition moderates or arrests chronic pain. The effect of the treatment was determined by a patient questionnaire and clinical assessment of the patients by a study physician.

The patient questionnaire asks the patient to assess his or her current level of pain using a linear visual analog scale of 10 where the pain is rated from 10, "pain as bad as it could be" to 0, "no pain". After taking the medications for several weeks, the patients are asked to indicate the current level of pain, as well as to indicate the degree of pain abatement using a linear visual analog pain relief scale of 10 rated from 10, no pain relief to complete 0, pain relief.

The DM dosage administered to the subjects of the study were a total daily dose up to 120 mg of DM, varying with the individual, taken in a capsule formulation in combination with quinidine. Quinidine was administered twice daily with DM up to a total daily dosage 150 mg, varying with the individual subject.

Patient #1 was a 73-year-old female, with a history of diabetes diagnosed ten years earlier. She reported burning and tingling of her feet for two years, which had been increasingly bothersome in the past year. The patient noticed the sensations particularly when she was walking or standing and also at night. The patient did not notice any similar sensations in her hands and denied any significant neck or back pain. The neurological exam was normal, except for the sensory portion of the exam which showed decreased appreciation of pinprick, light touch, and vibratory sense in her distal lower extremities. The neurophysiological assessment confirmed a diagnosis of sensorimotor polyneuropathy.

Prior to going on medication, the patient filled out a visual analog scale, describing her level of pain both on April 11 and shortly before beginning medication on April 25. The patient initially assessed her pain as 3–4 on the pain scale, with 10 indicating pain as bad as it could be. The patient started her medication shortly thereafter, taking 30 mg of dextromethorphan and 75 mg of quinidine once a day.

The follow up exam was give approximately a month later on May 9. The patient reported to be feeling better with much less pain. She noted the tingling in her feet and pain in her right leg was alleviated. Her sleep patterns were the same. She reported there were no side effects taking DM/quinidine at a dosage of 30 mg/75 mg twice a day. At that point her dosages were increased to 60 mg of dextromethorphan and 75 mg of quinidine twice a day.

Two weeks later on May 19, the patient filled out a visual analog pain relief scale, indicating that the level of pain was substantially improved, now rated as 1 to 2 with 10 rated as pain as bad as it could be, indicating that she had obtained significant pain relief. The overall impression was that her pain was much better. She reported feeling well with no side effects. The tingling had diminished compared to the past when it occurred 3 to 4 times per week. On May 23 the patient reported her level of pain as between 0 and 1, which 0 indicating not pain. The patient then stopped taking the DM/quinidine and reported back on May 27 that she was well without any significant return of pain. On May 31, 1994 she reported that the tingling in feet and hands had returned and she was not sleeping as well. The patient then requested to be placed back on the medication.

Patient #2 was a 53-year-old male with painful sensations on his right side. This patient had suffered from a stroke in 1991. A CT scan at the time showed a left posterior cerebral infarct. The patient also had coronary artery disease and bypass surgery in 1991, and suffered from diabetes and hypertension. Neurological findings included visual and sensory loss, and right-sided weakness. Over the past 4 to 5 months, the patient had noted a buzzing sensation on his right side and an icy or heat sensation, which affected the right side of his face, arm, chest and leg. His left side was unaffected. This unpleasant sensation was particularly bothersome at night occurring for up to five minutes at a time, and off and on all day long. The buzzing sensation was generally always present. The sensation was uncomfortable, not very painful at times, but caused the patient a great deal of anxiety. In addition, the patient has noted some tingling in the bottom of both feet from time to time, a high pitched hum in his ears and lightheadedness when his head was tipped back. In addition, this patient had reported tinnitus.

The patient was assessed by the examining physician as having classic symptoms of Dejerine-Roussy Syndrome, which is pain emanating from a diseased thalamus secondary to stroke.

The patient initially assessed his pain on the visual analog scale as varying between 9 and 10 at peak period to between 5 and 6 at other times, with 10 indicating pain as bad as it could be. Six weeks after being placed on the medication at a dosage of 30 mg DM/75 mg quinidine twice a day, the patient indicated pain at between 7 and 8 at peak times, with pain between 3 and 4 at other times using the visual analog scale. At this time, the patient indicated the level of pain relief as between 2 and 3, with 0 indicating complete pain relief, and 10 indicating no pain relief. One week after stopping the medications, the patient indicated a return to a pain level at between 7 and 8.

Patient #3 was a 63 year old male who had been diagnosed with diabetes for 25 years. He also suffered from arthritis and hypertension. The patient complained of numbness in his hands for two years. In addition, the patient noted that his feet hurt for the past three years. Throbbing pain interfered with sleep and required pain pills. He also had pain at the tip of his buttocks and intermittent neck pain. The neurological examination was remarkable for markedly decreased pinprick sensation in the patient's feed and distal fingers, with normal position sense and slightly decreased vibration sense. The clinical assessment was that the patient had primarily a sensory neuropathy secondary to his diabetes.

Prior to starting the DM-quinidine treatment at a dosage of 30 mg dextromethorphan and 75 mg quinidine at twelve hour intervals, the patient completed two visual analog scales describing his level of pain, one on April 11 and one shortly before beginning his medication on May 9. The patient initially rated his pain at between 5 and 6, and one month later as between 6 and 7, with 10 indicating the pain was as bad as it could be. The patient began taking DM-quinidine in the dosage of one tablet of 30 mg of dextromethorphan and 75 of quinidine twice a day.

On May 16 the patient noted via a telephone conversation that he felt lightheaded and his stomach was mildly upset, but he otherwise felt okay and he was continuing on the medication. The patient followed up in the office on May 23 and at that point, described that his pain was reduced from occurring nightly to only occurring occasionally, and was reduced overall to about 70–80% of what was previously experienced. He was not taking any other types of pain pills and had awakened only once at night from pain since being on the medication. He reported still having some intermittent light pain. Side effects were reported to be a little nausea, but not every day. At this time he rated his pain relief as between 1 and 2, with 0 indicating complete pain relief, and his current level of pain at between 1 and 2, with zero indicating no pain. The examining physician rated the patient's level of pain as much better.

On May 31 the patient reported pain in each foot during the previous week. He continued to take one tab of 30/75 DM/Quinidine. After two more weeks, he stopped taking the medication. On July 19, the patient completed another visual analog scale describing his current level of pain. He reported the level of pain as between 2 and 3, which remained lower that his initial assessment, even though he had discontinued his medication.

Example 8

Treatment of Tinnitus

Patient #2 from the pain study described in Example 7 also had suffered from chronic ringing in the ears, known as tinnitus, for a number of years. As a part of the pain study, this patient had taken 30 mg DM/75 mg quinidine capsules twice a day to relieve thalamic pain syndrome resulting from a stroke three years earlier. After about two weeks of taking the DM/quinidine capsules to relieve his pain, this patient reported an unexpected and total cessation of his chronic tinnitus. This evidence, together with published studies that NMDA receptors are found in the cochlear system which is the presumed site of the tinnitus disorder indicate that the DM/antioxidant combination is a promising therapy for tinnitus.

These examples demonstrate that the combination of dextromethorphan and an antioxidant such as quinidine are effective at treating intractable disorders, including intractable coughing, chronic pain, dermatitis, tinnitus and sexual dysfunction. Although this invention has been described with reference to the presently preferred embodiments, it is understood that various modifications can be made without departing from the spirit of the invention. According, the invention is limited only by the following claims.

We claim:

1. A method of increasing the effectiveness of dextromethorphan in treating chronic or intractable pain, comprising administering to a patient suffering from chronic or intractable pain a therapeutically effective dosage of dextromethorphan or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective dosage of a debrisoquin hydroxylase inhibitor.

2. The method of claim 1 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of quinidine, quinine, and pharmaceutically acceptable salts thereof.

3. The method of claim 2 wherein quinidine is administered at a dosage not exceeding about 300 milligrams per day.

4. The method of claim 1 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of disulfiram, fluoxetine, propranolol, nortriptyline, and pharmaceutically acceptable salts thereof.

5. A method of using dextromethorphan to treat chronic or intractable pain, comprising administering, to a patient suffering from chronic or intractable pain, dextromethorphan or a pharmaceutically acceptable salt thereof in combination with a debrisoquin hydroxylase inhibitor, wherein the dextromethorphan or salt thereof and the inhibitor are administered at combined dosages which render the dextromethorphan therapeutically effective in substantially reducing chronic or intractable pain, without causing unacceptable side effects.

6. The method of claim 5 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of quinidine, quinine, and pharmaceutically acceptable salts thereof.

7. The method of claim 6 wherein quinidine is administered at a dosage not exceeding about 300 milligrams per day.

8. The method of claim 5 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of disulfiram, fluoxetine, propranolol, nortriptyline, and pharmaceutically acceptable salts thereof.

9. A method of using dextromethorphan in treating tinnitus, comprising administering, to a patient suffering from tinnitus, dextromethorphan or a pharmaceutically acceptable salt thereof in combination with a debrisoquin hydroxylase inhibitor, wherein the dextromethorphan or salt thereof and the debrisoquin hydroxylase inhibitor are administered at combined dosages which render the dextromethorphan thereof therapeutically effective in substantially reducing tinnitus without causing unacceptable side effects.

10. The method of claim 9 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of quinidine, quinine, and pharmaceutically acceptable salts thereof.

11. The method of claim 10 wherein quinidine is administered at a dosage not exceeding about 300 milligrams per day.

12. The method of claim 9 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of disulfiram, fluoxetine, propranolol, nortriptyline, and pharmaceutically acceptable salts thereof.

13. A method for treating sexual dysfunction, comprising administering to a patient in need thereof dextromethorphan or a pharmaceutically acceptable salt thereof in combination with a debrisoquin hydroxylase inhibitor, at combined dosages which render the dextromethorphan thereof therapeutically effective in treating the sexual dysfunction.

14. The method of claim 13 wherein the patient is a male who suffers from priapism or premature ejaculation.

15. The method of claim 13 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of quinidine, quinine, and pharmaceutically acceptable salts thereof.

16. The method of claim 15 wherein quinidine is administered at a dosage not exceeding about 300 milligrams per day.

17. The method of claim 13 wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of disulfiram, fluoxetine, propranolol, nortriptyline, and pharmaceutically acceptable salts thereof.

18. A unit dosage formulation for treatment of chronic or intractable pain, comprising:

(a) dextromethorphan or a pharmaceutically acceptable salt thereof, and,

(b) a debrisoquin hydroxylase inhibitor, in a combined form that is designed for oral ingestion by humans, wherein the dextromethorphan or salt thereof and the debrisoquin hydroxylase inhibitor are present at a combined dosage which renders the dextromethorphan therapeutically effective in substantially reducing chronic or intractable pain, without causing unacceptable side effects.

19. The unit dosage formation of claim 18, comprising a digestible capsule which encloses the dextromethorphan or pharmaceutically acceptable salt thereof and the debrisoquin hydroxylase inhibitor.

20. The unit dosage formulation of claim 18, wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of quinidine, quinine, and pharmaceutically acceptable salts thereof.

21. The unit dosage formulation of claim 20, wherein the dosage of quinidine is 300 milligrams/day or less.

22. The unit dosage formulation of claim 18, wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of disulfiram, fluoxetine, propranolol, nortriptyline, and pharmaceutically acceptable salts thereof.

* * * * *

Exhibit E

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MAINTENANCE FEE STATEMENT

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5,863,927	$440.00	$0.00	02/11/02	08/464,792	01/26/99	09/19/96	04	YES	P-CN-1609

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
RE38,115	**$1,150.00**	**$0.00**	**04/06/06**	**10/052,698**	**01/26/99**	**09/19/96**	**08**	**YES**	**AVANIR.079RX**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
RE38,115	$2,055.00	$65.00	07/27/10	10/052,698	01/26/99	09/19/96	12	YES	018885-000710US

Exhibit F

Phase 3 Clinical Trials

Study Number	Study Title	Approx. Start	Approx. End
99-AVR-102	A Double-Blind Controlled, Multicenter Phase 2/3 Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Psedobulbar Affect in Patients with Amyotrophic Lateral Sclerosis	8/1/2001	6/20/202 (results announced)
02-AVR-106	A Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Multiple Sclerosis	12/2/2002	8/24/2004 (results announced)
02-AVR-107	An Open-Label, Multicenter Study to Assess the Safety of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Patients with Pseudobulbar Affect	3/15/2003	6/7/2007 (last patient out) *
07-AVR-123 DB And 07-AVR-123 OL**	A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy and to Determine the Pharmacokinetics of Two Doses of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Psedolbulbar Affect (PBA) in Patients with Amyotrophic Lateral Sclerosis and Multiple Sclerosis	12/13/07	11/10/09 (results announced)

* results of this long-term safety study and results were never ammounced, just submitted to FDA

** AVR-123 comprised a two-phase study with double blind (DB) and open-label (OL) treatment periods